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ART UNIT	**PAPER NUMBER**
1636	

NOTIFICATION DATE	DELIVERY MODE
11/20/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/830,669	MARLIERE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-104 and 106-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *86-89,91-102,108 and 110-118* is/are allowed.

6)☒ Claim(s) *103, 104, 107 and 109* is/are rejected.

7)☒ Claim(s) *90 and 106* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 8/24/2007, in which claims 97, 100, 103, 108, 109, 114 and 116 were amended. Currently, claims 86-104 and 106-118 are pending and under consideration.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Claim Objections

Claim 90 objected to because of the following informalities: the commas should be revised to set off the parenthetical elements to improve the grammar of the claim. Appropriate correction is required. This objection was made in the Office action mailed 4/24/2007.

Claim 106 is objected to because of the following informalities: the hyphen between the words "on" and "October" should be deleted in part (c) of the claim to improve the grammar of the claim. Appropriate correction is required. This objection was made in the Office action mailed 4/24/2007.

Response to Arguments - Claim Objections

Applicant's arguments filed 8/24/2007 have been fully considered but they are not persuasive. The response does not specifically address the objections to claims 90 and 106. Claim 90 should be amended to improve the grammar of the claim, and the hyphen should be deleted from claim 106. Appropriate correction is required in response to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 109 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection was made in the Office action mailed 4/24/2007 and has been rewritten to address the amendment to the claim in the reply filed 8/24/2007.

Claim 109 is vague and indefinite in that the metes and bounds of the phrase "wherein said culture medium in (b) allows the growth of said cell contains a precursor of said unconventional amino acid" are unclear. It is unclear if the medium or the cell contains the precursor of the unconventional amino acid.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 103, 104 and 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the Office action mailed 4/24/2007 and has been reiterated below.

The rejected claims are drawn to bacterial or yeast cells obtained by methods of selection wherein a missense mutation is incorporated into a an essential gene (required for growth of the host cell) at a target codon and the cell is grown under selective conditions wherein 1) the culture medium does not contain a nutrient that will compensate for the lack of a functional copy of the essential gene product, and 2) the culture medium contains an amino acid encoded by the target codon (prior to mutation). Further, the cell must comprise an valyl-tRNA synthetase which recognizes a given amino acid and which is capable of charging onto one of its associated tRNAs an unconventional amino acid or an amino acid other than said given amino acid, wherein the gene encoding the aminoacyl-tRNA synthetase contains at least one mutation compared with the sequence of the corresponding wild-type gene. The rejected claims thus comprise a set of yeast and bacterial cells that encompass a mutation in a valyl-tRNA synthetase gene of any bacteria or yeast cell, where the mutated valyl-tRNA synthetase is capable of mischarging a tRNA in the cell and suppressing a missense mutation in an essential gene.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes *E. coli* strains deposited at the CNCM under the Nos. I-2025, I-2026, I-2027, I-2339, I-2340, and I-2341, also referred to as strains β5366, β8144, β8146, β5479, β5485, and β5486, respectively (e.g. pages 7-9). Strain I-2025 (β5366) does not meet the structural or functional limitations of the claims in that the strain is incapable of growing without thymine or thymidine due to the absence of a mutation in any gene capable

of suppressing the missense mutation in the thyA gene (e.g. Example 1). Strains I-2026 and I-2027 contain the K277Q allele of the ValS gene (e.g. page 24, lines 23-25). Strain I-2339 contains the R223H allele of the ValS gene (e.g. page 8, lines 13-24). Strain I-2340 contains the V276A allele of the ValS gene (e.g. page 8, lines 25-34). Strain I-2341 contains the D230N allele of the ValS gene (e.g. page 9, lines 7-8). Thus, each of the strains described in the instant specification is a strain of *E. coli* with a missense mutation in the ValS gene. The specification does not describe mutations in any other *E. coli* aminoacyl-tRNA synthetase genes. The specification does not describe any mutations in an aminoacyl-tRNA synthetase gene of a cell isolated from any other type of organism, either yeast or bacteria. Further, the instant specification and prior art do not clearly describe what mutations in what functional domains of different aminoacyl-tRNA proteins will allow the mutated aminoacyl-tRNA synthetase to function in the manner recited in the rejected claims.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of *E. coli* strains with missense mutations in the ValS gene. The results are not necessarily predictive of other mutations that will confer the claimed function in other bacterial or yeast species. There is no evidence of record to indicate that a representative number of bacterial and yeast valyl-tRNA synthetase genes were know in the art at the time the invention was made. Thus, it is impossible for one to extrapolate from the few examples described herein those isolated cells that would necessarily meet the structural/functional characteristics of the rejected claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the genetic modifications required to confer the claimed function, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Given the very large genus of yeast and bacterial cells encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to genetic modifications of valyl-tRNA synthetase that meet the functional limitations of the claims for a representative number of bacterial and yeast organisms, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of isolated cells. Therefore, the

skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 103, 104 and 107.

Response to Arguments - 35 USC § 112

The rejection of claims 97-104, 106-108 and 110-118 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 8/24/2007.

With respect to the rejection of claim 109 under 35 U.S.C. 112, second paragraph, Applicant's arguments filed 8/24/2007 have been fully considered but they are not persuasive. The response asserts that the claims have been amended to obviate the rejection. However, it is still unclear if the medium or the cell contains the precursor of the unconventional amino acid. If Applicant intends for the precursor of the unconventional amino acid to be present in the medium, it would be remedial to amend the claim to replace the phrase "wherein said culture medium in (b) allows the growth of said cell contains a precursor of said unconventional amino acid" with the following: "wherein said culture medium in (b), which allows the growth of said cell, contains a precursor of said unconventional amino acid."

With respect to the rejection of claims 103, 104 and 107 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, Applicant's arguments filed 8/24/2007 have been fully considered but they are not persuasive.

The response provides evidence that a representative number of valyl-tRNA synthetase sequences of bacteria and yeast were known in the art at the time the invention was made and that the sequences demonstrate strong similarities throughout bacteria and yeast. Further, the

response asserts that the present specification provides a detailed description of the procedure for conducting the claimed method, which would allow one to practice the invention with routine experimentation.

Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895. Although one can practice the method of claim 86 without undue experimentation, the specification does not describe a representative number of members of the claimed genus that are capable of mischarging a tRNA in the cell to suppress a missense mutation in an essential gene. The specification does not describe which mutations in which functional domains of the valyl-tRNA synthetase genes or proteins will allow the mutated aminoacyl-tRNA synthetase to function in the manner recited in the claims. In the instant case, the specification describes the following *E. coli* cells: strains I-2026 and I-2027, which contain the K277Q allele of the ValS gene (e.g. page 24, lines 23-25); strain I-2339, which contains the R223H allele of the ValS gene (e.g. page 8, lines 13-24); strain I-2340, which contains the V276A allele of the ValS gene (e.g. page 8, lines 25-34); and strain I-2341, which contains the D230N allele of the ValS gene (e.g. page 9, lines 7-8). Each of the disclosed mutations in the *E. coli* ValS gene allow the encoded valyl-tRNA synthetase to charge onto one of its associated tRNAs cysteine, in a manner that allows the cell to suppress a missense mutation in an essential gene. The specification reasons that the valyl-tRNA synthetase mutants have a broadened specificity making them capable of charging $tRNAs^{Val}$ with compounds that show steric resemblance to valine, such as cysteine, L-2-aminobutyrate, L-2-aminovalerate, L-2,3-diaminoproprionate or L-3-thiol-2aminobutyrate (e.g., Examples 3 and 6). However, it is not

clear that the compounds, other than cysteine, are capable of producing a protein, wherein the amino acid sequence of the protein is mutated by comprising at least one unconventional amino acid, because the compounds appear to lack the structural elements necessary to form a peptide bond within a protein. Upon consideration of the references provided by Applicant in the response filed 8/24/2007, it is clear that the mutated residues disclosed in the present specification for *E. coli* valyl-tRNA synthetase are conserved in the valyl-tRNA synthetases of *Saccharomyces cerevisiae* (yeast) and other bacteria. Thus, one would expect that the same mutations could provide the structure necessary for the valyl-tRNA synthetases to charge a $tRNA^{Val}$ with cysteine. However, the claims encompass bacterial and yeast cells that comprise mutations in valyl-tRNA synthetase that allow charging of $tRNA^{Val}$ with any of the other 19 naturally occurring amino acids, as well as any other amino acid not normally incorporated by ribosomes during the biosynthesis of proteins synthesized by bacteria or yeast. The sequence alterations described in the present specification do not provide a representative number of embodiments to describe the structure necessary to confer the claimed function of being "capable of charging onto one of its associated tRNAs an unconventional amino acid other that said given amino acid." Without a correlation between structure and function, the claim does little more than define the claimed invention by function, except for those valyl tRNA synthetase mutations capable of charging a $tRNA^{Val}$ with cysteine.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Applicant's arguments, see page 12, filed 8/24/2007, with respect to the rejection of claim 106 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement

requirement, have been fully considered and are persuasive. The previous rejection of claim 106 has been withdrawn.

Conclusion

Claims 86-89, 91-102, 108 and 110-118 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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